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26 September 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BISUBSTITUTED CARBOCYCLIC CYCLOPHILIN BINDING COMPOUNDS AND THEIRUS

(57) Abstract: The present invention relates to novel, non-peptidic small organic compounds having an affinity for cyclophilin (CyP)-type immunophilin proteins. In the compounds of this invention, at least two carbo- or heterocyclic groups are attached to a central saturated, partially saturated, or aromatic 5-6 membered carbocyclic ring by a combination of straight or branched linker chains. The invention further relates to pharmaceutical compositions comprising one or more of the said compounds, and to the uses of these compounds and compositions for binding CyP-type proteins, inhibiting their peptidyl-prolyl isomerase activity, and for research, development, and therapeutic applications in a variety of medical disorders, such as neurological disorders, hair loss disorders, ischemic disorders, and disorders caused by viral or protozoan infection.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/44449

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C233/65 C07C235/24 C07C235/56 C07C275/30 C07C275/36
 C07C281/06 C07C309/73 C07C311/48 C07C311/49 C07C311/51
 C07C335/20 C07C333/16 C07C335/18 C07C335/42 C07C337/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 921 682 A (J.R. GEIGY) 20 March 1963 (1963-03-20) page 5, line 6 - line 8 page 5, line 10 - page 6, line 2 page 5, line 7 - line 8 page 5, line 11 - line 12 ---	1-3, 29
X	R.T. MAJOR: "Catalytic reduction of nitroaniline and paraphenylenediamine in the presence of aldehydes and ketones" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 53, no. 12, December 1931 (1931-12), pages 4373-4375, XP002205592 American Chemical Society, Washington, DC, US ISSN: 0002-7863 page 4375; table I --- -/-	1, 2, 4, 10, 13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

*** Special categories of cited documents:**

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

11 July 2002

Date of mailing of the international search report

25/07/2002

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/44449

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C337/08 C07D207/16 C07D271/10 C07D285/12 C07D333/24
 A61K31/18 A61K31/17 A61K31/167 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HITOSHI OINUMA, ET AL.: "Synthesis and biological evaluation of substituted benzenesulphonamides as novel potent membrane-bound phospholipase A2 inhibitors"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, no. 7, July 1991 (1991-07), pages 2260-2267, XP000602078</p> <p>American Chemical Society, Washington, DC, US</p> <p>ISSN: 0022-2623</p> <p>compounds 7b-7m, 7r-7w</p> <p style="text-align: center;">--- -/--</p>	1,2,4, 10,13

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *8* document member of the same patent family

Date of the actual completion of the international search

11 July 2002

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Name and mailing address of the ISA

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English, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/44449

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>M. REIFFEN, ET AL.: "Specific bradycardic agents. 1. Chemistry, pharmacology, and structure-activity relationships of substituted benzazepinones, a new class of compounds exerting antiischaemic properties"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 5, May 1990 (1990-05), pages 1496-1504, XP002205593</p> <p>American Chemical Society, Washington, DC, US</p> <p>ISSN: 0022-2623</p> <p>page 1504, right-hand column, line 15 - line 16</p> <p>page 1504, right-hand column, line 18</p> <p>page 1504, right-hand column, line 19 - line 20</p>	1,2,4,13
X	<p>F.O. RITTER: "Studies in the di-acyl acyl hydrazine series. III. The oxidation of acetylhydrazobenzene"</p> <p>JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 56, no. 4, April 1934 (1934-04), pages 975-976, XP002205594</p> <p>American Chemical Society, Washington, DC, US</p> <p>ISSN: 0002-7863</p> <p>page 976, right-hand column, line 3 - line 7</p>	1,2,4,13
X	<p>S.G. COHEN, ET AL.: "Preparation and kinetics of decomposition of a bicyclic azo compound. A novel reduction"</p> <p>JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 83, no. 7, 5 July 1961 (1961-07-05), pages 2895-2900, XP002205595</p> <p>American Chemical Society, Washington, DC, US</p> <p>ISSN: 0002-7863</p> <p>page 2899, right-hand column, line 14 - line 28</p>	1,7,8,10,14,24
X	<p>C. KING: "Cyclopolymerisation of aliphatic 1,2-diisocyanates"</p> <p>JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 86, no. 3, 5 February 1964 (1964-02-05), pages 437-440, XP002205596</p> <p>American Chemical Society, Washington, DC, US</p> <p>ISSN: 0002-7863</p> <p>table III, entry 5</p>	1,5,6,9,10,14,15

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/44449

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 075 166 A (MONSANTO CHEMICALS) 12 July 1967 (1967-07-12) examples 1,2 ---	1-4,10, 14
X	US 3 062 813 A (F.L. SCOTT) 6 November 1962 (1962-11-06) examples 1,2,5,10 ---	1,2,4,13
P,X	WO 01 17953 A (GUILFORD PHARMACEUTICALS) 15 March 2001 (2001-03-15) the whole document ---	1-84
A	WO 98 37882 A (GUILFORD PHARMACEUTICALS) 3 September 1998 (1998-09-03) the whole document -----	1-84

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/44449

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-27 (partially), 28, 29 30-84 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1-27 (partially), 28, 29 30-84 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which part(s) of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and /or to issue a complete search report over the whole breadth of the claim(s). The search and the report for those claims can only be considered complete for compounds 1-45 and their use as well as the compounds defined by Formula VII in claim 28 and their use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/44449

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
GB 921682	A	20-03-1963	CH	364384 A	30-05-1962
			CH	362068 A	31-05-1962
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